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Asymmetric syntheses of 6-deoxyfagomin, D-deoxyrhamnojirimycin, and D-rhamnono-1,5-lactam

Rui Fu [a], Yu Du [a], Zhao-Ying Li [a], Wei-Xuan Xu [a], Pei-Qiang Huang [a,b,*]

[a] Department of Chemistry and Key Laboratory for Chemical Biology of Fujian Province, College of Chemistry and Chemical Engineering, Xiamen University, Xiamen, Fujian 361005, PR China
[b] State Key Laboratory of Bioorganic and Natural Products Chemistry, 354 Fenglin Lu, Shanghai 200032, PR China

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ABSTRACT

N-Allyl protected 3-*O*-benzyloxglutarimide **11** was synthesized as a useful variant of the chiral building block **10**. This modification allowed a high-yielding deprotection of the allyl group from the lactam intermediate **14**. Starting from this building block, the asymmetric syntheses of aza-sugars 6-deoxyfagomine (**2**), D-rhamnono-1,5-lactam (**6**), as well as D-deoxyrhamnojirimycin (**5**) have been achieved in high regio- and/or diastereo-controlled manner.

1. Introduction

Aza-sugars (also known as iminosugars) are polyhydroxylated alkaloids with either five- or six-membered, mono- or bi-cyclic structures.[1] Being 'nitrogen-in-the-ring' analogs of pyranoses and furanoses, many aza-sugars were found to be potent inhibitors of carbohydrate-processing enzymes involved in important biological systems. Consequently, they are promising for the treatment of metabolite disorder-associated diseases such as diabetes, cancer, AIDS, and viral infections.[1] Indeed, Miglitol[2] and Zavesca[3] (Miglustat) have been launched on market as drugs for the treatment of Type II diabetes and Gaucher's disease, respectively.

Fagomine[4,5] (**1**) and 6-deoxyfagomine[4] (**2**) (Fig. 1) are two polyhydroxylated piperidine alkaloids isolated from *Lycium chinense* (Solanaceae) roots. Before that, the occurrence of fagomine[5] and its stereoisomers in the leaves of *Xanthocercis zuinbesiaca* (Leguminosae) has already been reported.[5a] Fagomine and 3-*epi*-fagomine were shown to have activities against mammalian α-glucosidase and β-galactosidase,[5a] and have a potent antihyperglycaemic effect in streptozocin-induced diabetic mice and a potentiation of glucose-induced insulin secretion.[5b] 1,6-Dideoxynojirimycin (**3**) was isolated as a new sugar-mimic alkaloid from the Pods of *Angylocalyx pynaertii*.[6] α-Homo-L-rhamnojirimycin **4** is an effective inhibitor of naringinase.[7] In addition, D-deoxyrhamnojirimycin (DRJ) (**5**),[8a,b] and its enantiomer L-deoxyrhamnojirimycin (LRJ),[8b,c] and D-rhamnono-1,5-lactam[8b] (**6**) have also been synthesized for biological test. The synthesis of aza-sugars, their stereoisomers, and analogs have attracted considerable attention, and a number of methods have been developed.[1]

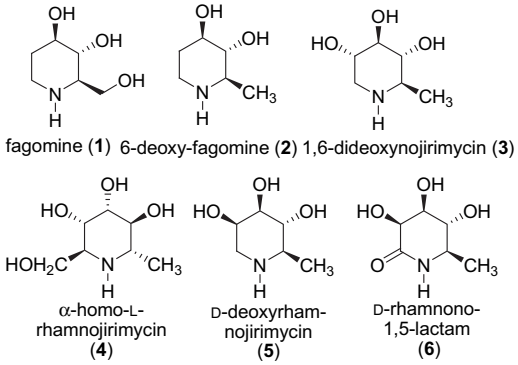

Figure 1.

In continuation of our study on the development of protected 3-hydroxyglutarimide-based synthetic methodology,[9] we wish to report *N*-allyl protected 3-*O*-benzyloxyglutarimide **11** as

* Corresponding author. Fax: +86 592 2186400.
E-mail address: pqhuang@xmu.edu.cn (P.-Q. Huang).

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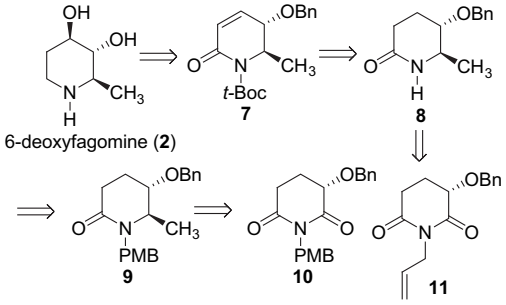
a beneficial variant of the building block **10**, and its application to the enantioselective syntheses of 6-deoxyfagomine (**2**), D-rhamnono-1,5-lactam (**6**), and D-deoxyrhamnojirimycin (**5**).

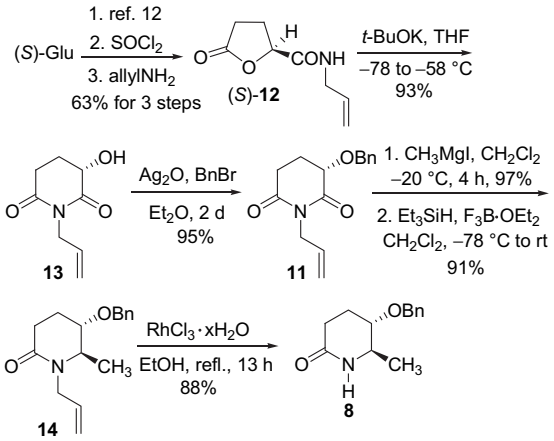
2. Results and discussion

The retrosynthetic analysis of 6-deoxyfagomine (**2**) is outlined in Scheme 1, which featured the introduction of the hydroxyl group at C-4 via the α,β-unsaturated mixed imide **7**. The latter was envisioned to be prepared from lactam **9**,[10] which is available from the known building block **10**. In practicing this plan, it was observed that the ceric ammonium nitrate (CAN)-mediated oxidative cleavage of the *p*-methoxybenzyl group (PMB) in lactam **9** produced lactam **8** in only 60% yield. We decided to develop the *N*-allyl protected[11] glutarimide derivative **11** as an improved building block for our general synthetic program.[9]



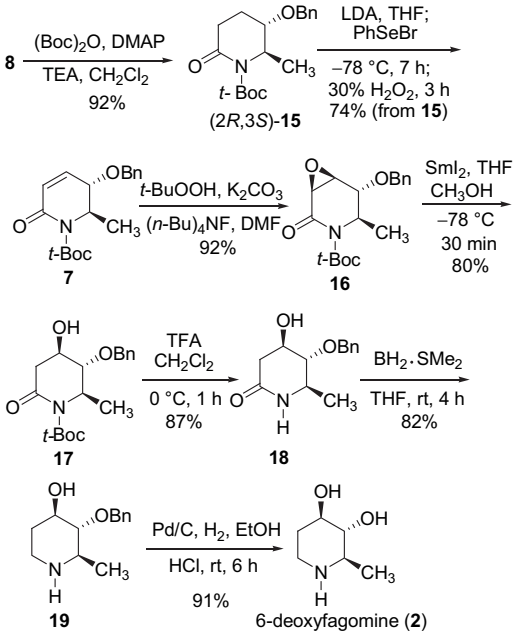
Scheme 1.

The building block **11** was synthesized from (*S*)-glutamic acid and allylamine by the method established previously,[10,12] namely, diazodation, lactone-amide formation, ring expansion, and *O*-benzylation (Scheme 2). Methyl magnesium iodide addition, followed by boron trifluoride etherate-mediated reductive dehydroxylation with triethylsilane produced lactam **14** in excellent regio- and diastereo-selectivities. The stereochemistry of the major diastereomer **14** was tentatively assigned as *trans* on the basis of the observed vicinal coupling constant ($J_{5,6}$=1.4 Hz; cf. *N*-PMB protected analog: $J_{5,6}$=1.5 Hz for *trans*-diastereomer,[10a] and $J_{5,6}$=4.6 Hz for *cis*-diastereomer[10c]), that was confirmed after final conversion of **14** into the natural product 6-deoxyfagomine (**2**). Cleavage of the lactam *N*-allyl group was achieved by heating **14** with rhodium trichloride hydrate, in refluxing ethanol,[13] which afforded lactam **8** in 88% yield.



Scheme 2.

To introduce the carbon–carbon double bond, lactam **8** was converted into its activated form, namely, the mixed imide (2*R*,3*S*)-**15**, by the reaction with $(Boc)_2O$ [DMAP (cat.), TEA, CH_2Cl_2]. Successive treatment of **15** with LDA (THF, −78 °C) and PhSeBr produced an α-phenylselenide derivative,[14] which, without purification, was subjected to oxidation with H_2O_2 in wet CH_2Cl_2 at rt to give directly **7** in 74% overall yield from compound **15** (Scheme 3). For the introduction of the hydroxyl group at C-4, an epoxidation–regioselective SmI_2 reduction[15] procedure was envisioned. Thus, in the presence of tetrabutyl ammonium fluoride, and potassium carbonate, α,β-unsaturated mixed imide **7** was treated with *tert*-butyl hydroperoxide (TBHP) in DMF[15a,16] to furnish epoxide **16** as a single diastereomer in 92% yield. The stereochemistry of the product was assumed to be *trans* with respect to OBn group on the basis of the steric effect of the benzyloxyl group in the epoxidation,[17] that was confirmed after its transformation into the natural product **2**. Reductive ring-opening of the epoxide **16** with samarium diiodide[15] yielded regioselectively the 4-hydroxy-2-piperidinone derivative **17** in high yield. Compound **17** was subjected successively to *N*-deprotection with TFA, lactam reduction with borane dimethyl sulfide complex, and *O*-debenzylation under catalytic hydrogenolytic conditions to give 6-deoxyfagomine (**2**) in high overall yield. The physical {$[\alpha]_D^{20}$ −10.8 (*c* 0.4, H_2O); lit.[4] $[\alpha]_D^{20}$ −11.1 (*c* 0.1, H_2O)} and spectroscopic data of our synthetic compound were in agreement with those reported for the natural product.[4]



Scheme 3.

To further explore the possibility to use mixed imide **7** for the synthesis of other aza-sugars such as **4**, **5**, and **6**, the dihydroxylation of **7** was investigated. In the presence of 1.5 molar equiv of citric acid, treatment of α,β-unsaturated lactam **7** with the co-oxidant system OsO_4 (cat.)–NMO in a mixed solvent system[18] (*t*-BuOH/H_2O, 1:1) at rt for 18 h produced the dihydroxylated product **20** as a single diastereomer in 76% yield (Scheme 4). Stirring compound **20** with CF_3CO_2H in CH_2Cl_2 cleaved the Boc group to give lactam **21** in 90% yield. Hydrogenolysis of lactam **21** in the presence of 10%Pd(OH)$_2$/C led to the target molecule D-rhamnono-1,5-lactam (**6**) in 92% yield. The physical and spectroscopic data of the synthetic compound were in agreement with those of natural product {$[\alpha]_D^{20}$ −15.6 (*c* 0.4, H_2O) {lit.[8b] $[\alpha]_D^{20}$ −16.6 (*c* 0.27, H_2O)}.

On the other hand, reduction of lactam **21** with $BH_3 \cdot SMe_2$ in THF at rt for 4 h gave piperidine **22** in 97% yield (Scheme 5). Subjection of **22** to catalytic hydrogenolytic conditions (H_2, 10%Pd/C) led to D-deoxyrhamnojirimycin (**5**) in 70% yield. The physical and